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Can Preoperative PET/CT SUVmax Predict Aggressive Pathological Features in Non-Small Cell Lung Cancer? A Retrospective Cohort Study of STAS, LVI, and VPI

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Abstract

Background

Spread through air spaces (STAS), lymphovascular invasion (LVI), and visceral pleural invasion (VPI) are adverse prognostic features in non-small cell lung cancer (NSCLC) that can only be assessed postoperatively. This study evaluated whether preoperative primary tumor SUVmax on 18F-FDG PET/CT independently predicts these features.

Methods

In this retrospective cohort of 478 patients undergoing surgical resection for NSCLC, associations between primary tumor SUVmax and STAS, LVI, and VPI were assessed using univariate and multivariable logistic regression, adjusted for tumor size, histologic subtype, and other clinically relevant covariates. Discriminative performance was evaluated using receiver operating characteristic (ROC) curve analysis.

Results

STAS, LVI, and VPI were present in 269 (56.3%), 237 (49.6%), and 202 (42.3%) patients, respectively. SUVmax was independently associated with all three outcomes: STAS (adjusted OR = 1.051, 95% CI 1.020–1.083, p = 0.001), LVI (adjusted OR = 1.083, 95% CI 1.048–1.119, p < 0.001), and VPI (adjusted OR = 1.044, 95% CI 1.015–1.073, p = 0.002). Discriminative performance was acceptable for LVI (AUC = 0.701) but weak for STAS (AUC = 0.578) and VPI (AUC = 0.584). Sensitivity analyses excluding neoadjuvant-treated patients and interaction testing confirmed these associations were independent of neoadjuvant treatment status.

Conclusion

Preoperative SUVmax is independently associated with STAS, LVI, and VPI in resected NSCLC, most strongly for LVI. Although its standalone discriminative value is limited, SUVmax—already available at diagnosis—may contribute to multivariable preoperative risk stratification alongside histologic subtype and tumor size.

INTRODUCTION

Lung cancer remains the most commonly diagnosed malignancy and the leading cause of cancer-related death worldwide, accounting for approximately 2.6 million new cases and 1.9 million deaths in 2024 [1]. Non-small cell lung cancer (NSCLC) accounts for the majority of these cases, and surgical resection with curative intent remains the standard treatment for early-stage resectable disease.

However, even after complete resection, a substantial proportion of patients experience recurrence, and outcomes vary considerably among patients with the same pathological stage, indicating that anatomical staging alone does not fully capture tumor biological aggressiveness [2].

Among histopathological features associated with aggressive NSCLC behavior, spread through air spaces (STAS), lymphovascular invasion (LVI), and visceral pleural invasion (VPI) are well-established adverse prognostic factors, each independently associated with increased recurrence and worse survival [3–7]; VPI is additionally incorporated into the TNM T-category, upstaging small tumors from T1 to T2a [8]. However, all three can currently only be determined on postoperative histopathological examination, and are therefore unavailable when decisions on resection extent or adjuvant therapy are made. A reliable preoperative surrogate could therefore directly inform surgical planning, particularly for patients considered for limited resection.

18F-fluorodeoxyglucose (FDG) PET/CT is now routinely performed for preoperative staging in NSCLC. The maximum standardized uptake value (SUVmax) of the primary tumor, a semiquantitative measure of glucose metabolism, is generated automatically during this examination at no additional cost or delay. A high SUVmax has been consistently associated with worse survival in NSCLC, including after surgical resection, reflecting the link between increased metabolic activity and aggressive tumor biology [9, 10]. Because SUVmax is already available at diagnosis—before histopathological features are known—it represents an attractive candidate as a a noninvasive preoperative predictor for the adverse features described above.

Several studies have linked primary tumor SUVmax to individual adverse pathological features in NSCLC. Elevated SUVmax has been reported as an independent predictor of STAS [11, 12], and a positive relationship has been shown between SUVmax and a composite measure of pathological invasiveness including lymph node metastasis, VPI, and LVI [13]. However, most studies have examined these features separately, in different populations, with heterogeneous covariate adjustment, and rarely within the same surgical cohort. It therefore remains unclear whether SUVmax retains independent predictive value for STAS, LVI, and VPI when evaluated concurrently in the same cohort with consistent covariate adjustment.

The aim of this study was to evaluate the association between preoperative primary tumor SUVmax and the presence of STAS, LVI, and VPI in patients undergoing lung resection for NSCLC.

PATIENTS AND METHODS

Study Population

This retrospective study included 540 patients who underwent pulmonary resection (wedge resection or anatomical resection) for primary lung cancer between January 2021 and April 2026. Patients with a diagnosis of small cell lung carcinoma (n = 10), those without an available preoperative PET/CT within a clinically appropriate interval prior to surgery (n = 22), and those whose postoperative pathology reports

lacked data on STAS, LVI, or VPI (n = 30) were excluded. After these exclusions, 478 patients were included in the final analysis. The patient selection process is summarized in Fig. 1.

PET/CT Imaging

All patients underwent whole-body (vertex-to-thigh) F-18 fluorodeoxyglucose (FDG) PET/CT as part of routine preoperative staging, performed in the Department of Nuclear Medicine using standard institutional protocols. SUVmax values were extracted retrospectively from the original clinical PET/CT reports and were not re-measured for this study. Because PET/CT was performed preoperatively as part of routine care, SUVmax assessment preceded surgical resection and pathological evaluation. For patients who received neoadjuvant therapy, the SUVmax value from the post-treatment restaging PET/CT, rather than the pretreatment scan, was used in the analysis.

Surgical Procedure

All patients underwent anatomical or non-anatomical pulmonary resection, including wedge resection, segmentectomy, lobectomy, bilobectomy, or pneumonectomy. Lymph node sampling was performed in all patients. Surgery was performed via open thoracotomy, a hybrid approach, or video-assisted thoracoscopic surgery (VATS), according to surgeon preference and clinical circumstances.

Pathological Evaluation

STAS, LVI, and VPI status, together with histological subtype, tumor size, and lymph node involvement, were extracted from the original postoperative histopathological reports issued by the Department of Pathology as part of routine clinical care and reviewed and signed by two pathologists. VPI was graded using the standard PL0–PL3 system on hematoxylin and eosin (H&E)-stained sections, supplemented by elastic stains when needed to confirm invasion beyond the elastic layer; STAS and LVI were assessed on H&E sections using standard morphological criteria. Because this was a retrospective analysis of archived reports rather than a centralized slide re-review, the specific staining protocol applied in each case could not be independently verified or standardized.

Staging

Pathological staging was performed according to the 9th edition of the TNM Classification for Lung Cancer.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test;

continuous variables were expressed as mean ± SD or median (IQR) according to distribution, and categorical variables as frequencies and percentages.

Comparisons between patients with and without STAS, LVI, and VPI were performed separately, using the independent-samples t-test or Mann–Whitney U test for continuous variables, and the Pearson chi-square test or Fisher's exact test (when expected cell counts were < 5) for categorical variables.

Variables with $p < 0.10$ on univariable analysis were entered into multivariable logistic regression models to identify independent predictors of STAS, LVI, and VPI. Histological subtype was dichotomized as adenocarcinoma versus non-adenocarcinoma to avoid sparse categories, consistent with STAS's predominant association with adenocarcinoma in prior studies; smoking exposure was represented by pack-years rather than smoking status to better quantify cumulative tobacco exposure.

Prior to multivariable analyses, correlations among continuous predictors were evaluated using Spearman's rank correlation coefficient, and multicollinearity was assessed using tolerance, variance inflation factors (VIF), and condition indices; no evidence of problematic multicollinearity was identified. Goodness-of-fit was evaluated using the Hosmer–Lemeshow test, and model performance was assessed using the Nagelkerke R^2 statistic. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of primary tumor SUVmax to predict STAS, LVI, and VPI. The area under the curve (AUC) with 95% confidence intervals was calculated, and the optimal SUVmax cutoff was determined using the Youden index. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Patient and tumor characteristics

A total of 478 patients with non-small cell lung cancer were included (mean age 65.54 ± 9.66 years; 352 [73.6%] male). Most patients were current or former smokers (416, 87.0%; mean 39.60 ± 27.24 pack-years), and 402 (84.1%) had at least one comorbidity; 35 (7.3%) received neoadjuvant therapy. Surgical approach was thoracotomy in 204 (42.7%), VATS in 143 (29.9%), and hybrid in 131 (27.4%) patients, with lobectomy the most common resection (279, 58.4%). Adenocarcinoma was the predominant histology (259, 54.2%), followed by squamous cell carcinoma (156, 32.6%); most patients had stage I disease (267, 55.9%). Mean tumor size was 30.18 ± 19.29 mm and mean SUVmax was 9.94 ± 8.02. STAS, LVI, and VPI were present in 269 (56.3%), 237 (49.6%), and 202 (42.3%) patients, respectively. Postoperative complications occurred in 156 (32.6%) patients, with mean chest-tube duration of 5.21 ± 4.41 days and hospital stay of 6.32 ± 4.32 days. Detailed baseline characteristics are presented in Table 1.

Table 1
Baseline Demographic, Clinical, and Pathological Characteristics of the Study Cohort (n = 478)

Characteristic	Total cohort (n = 478)
Continuous variables, mean ± SD	
Age (years)	**65.54 ± 9.66**
Pack-years	**39.60 ± 27.24**
SUVmax	**9.94 ± 8.02**
Pathologic tumor size (mm)	**30.18 ± 19.29**
Radiologic mass size on PET/CT (mm)	**30.46 ± 19.22**
Chest-tube drainage duration (days)	**5.21 ± 4.41**
Length of hospital stay (days)	**6.32 ± 4.32**
Categorical variables, n (%)	
Sex	
Female	126 (26.4)
Male	352 (73.6)
Smoking history	
No	62 (13.0)
Yes	416 (87.0)
Comorbidity	
No	76 (15.9)
Yes	402 (84.1)
Neoadjuvant therapy	
No	443 (92.7)
Yes	35 (7.3)
Surgical approach	
Thoracotomy	204 (42.7)
Hybrid	131 (27.4)

SD: standard deviation; SUVmax: maximum standardized uptake value; PET/CT: positron emission tomography/computed tomography; VATS: video-assisted thoracoscopic surgery; STAS: spread through air spaces; LVI: lymphovascular invasion; VPI: visceral pleural invasion. Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). No data were missing for any variable (valid n = 478).

Characteristic	Total cohort (n = 478)
Continuous variables, mean ± SD	
Age (years)	**65.54 ± 9.66**
VATS	143 (29.9)
Type of resection	
Wedge resection	132 (27.6)
Segmentectomy	11 (2.3)
Lobectomy	279 (58.4)
Bilobectomy	20 (4.2)
Pneumonectomy	36 (7.5)
Histologic type	
Adenocarcinoma	259 (54.2)
Squamous cell carcinoma	156 (32.6)
Neuroendocrine tumor	36 (7.5)
Other	27 (5.6)
Stage group	
I	267 (55.9)
II	118 (24.7)
III	66 (13.8)
IV	27 (5.6)
Pathological features	
STAS positive	269 (56.3)
LVI positive	237 (49.6)
VPI positive	202 (42.3)
Surgical complication	
No	322 (67.4)

SD: standard deviation; SUVmax: maximum standardized uptake value; PET/CT: positron emission tomography/computed tomography; VATS: video-assisted thoracoscopic surgery; STAS: spread through air spaces; LVI: lymphovascular invasion; VPI: visceral pleural invasion. Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). No data were missing for any variable (valid n = 478).

Characteristic	Total cohort (n = 478)
Continuous variables, mean ± SD	
Age (years)	**65.54 ± 9.66**
Yes	156 (32.6)

SD: standard deviation; SUVmax: maximum standardized uptake value; PET/CT: positron emission tomography/computed tomography; VATS: video-assisted thoracoscopic surgery; STAS: spread through air spaces; LVI: lymphovascular invasion; VPI: visceral pleural invasion. Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). No data were missing for any variable (valid n = 478).

Predictors of spread through air spaces (STAS)

Univariate analysis

Spread through air spaces was identified in 269 of 478 patients (56.3%). Patients with STAS had higher SUVmax (10.82 ± 8.36 vs. 8.82 ± 7.42, p = 0.003) (Fig. 2) and greater smoking exposure (42.47 ± 28.28 vs. 35.91 ± 25.45 pack-years, p = 0.023) than those without. STAS was more frequent in adenocarcinoma than non-adenocarcinoma histology (61.8% vs. 49.8%, p = 0.008), while neoadjuvant therapy was associated with lower STAS prevalence (31.4% vs. 58.2%, p = 0.002). Tumor size showed a non-significant trend toward larger values in STAS-positive patients (p = 0.085); age, sex, comorbidity, surgical approach, and stage were not significantly associated with STAS (all p > 0.05). Detailed comparisons are in Table 2.

Table 2
Univariate Comparison of Categorical and Continuous Variables According to STAS Status (n = 478)

Variable / Category	STAS Negative (n = 209)	STAS Positive (n = 269)	p
Categorical variables, n (%)			
Sex			**0.216**
Female	61 (48.4)	65 (51.6)	
Male	148 (42.0)	204 (58.0)	
Comorbidity			**0.485**
No	36 (47.4)	40 (52.6)	
Yes	173 (43.0)	229 (57.0)	
Neoadjuvant therapy			**0.002**
No	185 (41.8)	258 (58.2)	
Yes	24 (68.6)	11 (31.4)	
Surgical approach			**0.938**
Thoracotomy	88 (43.1)	116 (56.9)	
Hybrid	59 (45.0)	72 (55.0)	
VATS	62 (43.4)	81 (56.6)	
Histologic type[a]			**0.008**
Other	110 (50.2)	109 (49.8)	
Adenocarcinoma	99 (38.2)	160 (61.8)	
Stage group			**0.200**
I	127 (47.6)	140 (52.4)	
II	43 (36.4)	75 (63.6)	
III	29 (43.9)	37 (56.1)	
IV	10 (37.0)	17 (63.0)	

SD: standard deviation; SUVmax: maximum standardized uptake value. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

[a] *Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=7.538, df = 3, p = 0.057). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).*

Variable / Category	STAS Negative (n = 209)	STAS Positive (n = 269)	p
Categorical variables, n (%)			
Sex			**0.216**
Continuous variables, mean ± SD			
Age (years)	65.25 ± 10.92	65.77 ± 8.56	**0.764**
Pack-years	35.91 ± 25.45	42.47 ± 28.28	**0.023**
SUVmax	8.82 ± 7.42	10.82 ± 8.36	**0.003**
Tumor size (mm)	29.23 ± 20.47	30.92 ± 18.33	**0.085**

SD: standard deviation; SUVmax: maximum standardized uptake value. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

[a] *Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=7.538, df = 3, p = 0.057). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).*

Multivariable analysis

Variables associated with STAS at p < 0.10, together with clinically relevant covariates, were entered into a multivariable model (SUVmax, pack-years, tumor size, neoadjuvant therapy, adenocarcinoma vs. other). SUVmax (adjusted OR = 1.051, 95% CI 1.020–1.083, p = 0.001), pack-years (OR = 1.009, 95% CI 1.001–1.016, p = 0.021), neoadjuvant therapy (OR = 0.288, 95% CI 0.133–0.621, p = 0.002), and adenocarcinoma histology (OR = 2.243, 95% CI 1.485–3.386, p < 0.001) remained independently associated with STAS; tumor size did not (OR = 1.002, 95% CI 0.991–1.013, p = 0.718) (Fig. 3). The model was globally significant (omnibus χ^2=39.227, df = 5, p < 0.001) and well calibrated (Hosmer-Lemeshow p = 0.926; Nagelkerke R^2=0.106). Crude and adjusted ORs are in Table 3.

Table 3
Univariate (Crude) and Multivariable (Adjusted) Logistic Regression Analysis for STAS (n = 478)

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
SUVmax	1.033 (1.009–1.059)	0.007	1.051 (1.020–1.083)	**0.001**
Pack-years	1.009 (1.002–1.016)	0.010	1.009 (1.001–1.016)	0.021
Tumor size (mm)	1.005 (0.995–1.014)	0.342	1.002 (0.991–1.013)	0.718
Neoadjuvant therapy (yes)	0.329 (0.157–0.688)	0.003	0.288 (0.133–0.621)	**0.002**
Adenocarcinoma (vs other)	1.631 (1.133–2.349)	0.009	2.243 (1.485–3.386)	**< 0.001**
Variables not included in the multivariable model				
Age	1.006 (0.987–1.025)	0.559	—	—
Sex (male vs female)	1.294 (0.860–1.946)	0.217	—	—
Comorbidity (yes vs no)	1.191 (0.729–1.948)	0.485	—	—
Surgical approach[a] (ref: VATS)				
Thoracotomy vs VATS	1.009 (0.655–1.553)	0.968	—	—
Hybrid vs VATS	0.934 (0.580–1.506)	0.779	—	—
Stage group[b] (ref: Stage I)				
Stage II vs I	1.582 (1.014–2.470)	0.043	—	—

CI: confidence interval; OR: odds ratio; VATS: video-assisted thoracoscopic surgery. Crude OR was derived from univariate logistic regression models including each variable individually. Adjusted OR was derived from the multivariable model including SUVmax, pack-years, tumor size, neoadjuvant therapy, and histologic type (adenocarcinoma vs. other) simultaneously. —: variable not included in the multivariable model.

[a] *The omnibus Wald test for surgical approach was not significant (p = 0.938).*

[b] *The omnibus Wald test for stage group was not significant (p = 0.203).*

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
Stage III vs I	1.157 (0.673–1.990)	0.597	—	—
Stage IV vs I	1.542 (0.681–3.492)	0.299	—	—

CI: confidence interval; OR: odds ratio; VATS: video-assisted thoracoscopic surgery. Crude OR was derived from univariate logistic regression models including each variable individually. Adjusted OR was derived from the multivariable model including SUVmax, pack-years, tumor size, neoadjuvant therapy, and histologic type (adenocarcinoma vs. other) simultaneously. —: variable not included in the multivariable model.

[a] *The omnibus Wald test for surgical approach was not significant (p = 0.938).*

[b] *The omnibus Wald test for stage group was not significant (p = 0.203).*

Sensitivity and interaction analyses

A sensitivity analysis excluding patients who received neoadjuvant therapy (n = 443), whose SUVmax was obtained from post-treatment restaging PET/CT, showed the SUVmax–STAS association remained essentially unchanged (adjusted OR = 1.050, 95% CI 1.017–1.083, p = 0.003; Hosmer-Lemeshow p = 0.856). An interaction term (SUVmax × neoadjuvant therapy) was not significant (Wald p = 0.584; LR χ^2=0.316, df = 1, p = 0.574), indicating the association was consistent regardless of neoadjuvant status.

Multicollinearity assessment

Among the continuous predictors, Spearman's rank correlation revealed a moderate correlation between SUVmax and pathologic tumor size (rho = 0.537, p < 0.001), with weaker correlations for the remaining pairs (all |rho|≤0.232); this correlation pattern was consistent across the STAS, LVI, and VPI models. No problematic multicollinearity was identified among the covariates of the multivariable model (all VIF < 1.4, tolerance > 0.70; highest condition index 6.73).

ROC analysis

Although SUVmax was independently associated with STAS, its standalone discriminative ability was weak (AUC = 0.578, 95% CI 0.526–0.630, p = 0.003), indicating it should be interpreted alongside other clinicopathological factors rather than as an independent classifier (Fig. 4). A Youden-based cutoff was nonetheless calculated for completeness: SUVmax ≥ 4.7 gave the optimal sensitivity-specificity balance (74.7%/39.2%; Youden index 0.140), though this should be interpreted cautiously given SUVmax's limited discriminative capacity for STAS.

Predictors of lymphovascular invasion (LVI)

Univariate analysis

Lymphovascular invasion was present in 237 of 478 patients (49.6%). LVI-positive patients had markedly higher SUVmax (12.44 ± 8.72 vs. 7.49 ± 6.38, $p < 0.001$) (Fig. 2) and larger tumor size (33.75 ± 18.43 vs. 26.67 ± 19.51 mm, $p < 0.001$) than LVI-negative patients. LVI was also associated with male sex (55.7% vs. 32.5% of women, $p < 0.001$), non-adenocarcinoma histology ($p = 0.005$), higher tumor stage ($p < 0.001$), and surgical approach ($p = 0.013$). Age, comorbidity, and neoadjuvant therapy were not significantly associated with LVI; pack-years showed a borderline difference ($p = 0.096$). Detailed comparisons are in Table 4.

Table 4
Univariate Comparison of Categorical and Continuous Variables According to LVI Status (n = 478)

Variable / Category	LVI Negative (n = 241)	LVI Positive (n = 237)	p
Categorical variables, n (%)			
Sex			**< 0.001**
Female	85 (67.5)	41 (32.5)	
Male	156 (44.3)	196 (55.7)	
Comorbidity			**0.406**
No	35 (46.1)	41 (53.9)	
Yes	206 (51.2)	196 (48.8)	
Neoadjuvant therapy			**0.200**
No	227 (51.2)	216 (48.8)	
Yes	14 (40.0)	21 (60.0)	
Surgical approach			**0.013**
Thoracotomy	87 (42.6)	117 (57.4)	
Hybrid	73 (55.7)	58 (44.3)	
VATS	81 (56.6)	62 (43.4)	
Histologic type			**0.005**
Other	95 (43.4)	124 (56.6)	
Adenocarcinoma	146 (56.4)	113 (43.6)	
Stage group			**< 0.001**
I	165 (61.8)	102 (38.2)	
II	39 (33.1)	79 (66.9)	
III	26 (39.4)	40 (60.6)	

SD: standard deviation; SUVmax: maximum standardized uptake value; VATS: video-assisted thoracoscopic surgery; LVI: lymphovascular invasion. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

 Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=13.517, df = 3, p = 0.004). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).

Variable / Category	LVI Negative (n = 241)	LVI Positive (n = 237)	p
Categorical variables, n (%)			
Sex			**< 0.001**
IV	11 (40.7)	16 (59.3)	
Continuous variables, mean ± SD			
Age (years)	65.72 ± 10.47	65.36 ± 8.78	**0.317**
Pack-years	37.25 ± 26.71	42.00 ± 27.62	**0.096**
SUVmax	7.49 ± 6.38	12.44 ± 8.72	**< 0.001**
Tumor size (mm)	26.67 ± 19.51	33.75 ± 18.43	**< 0.001**

SD: standard deviation; SUVmax: maximum standardized uptake value; VATS: video-assisted thoracoscopic surgery; LVI: lymphovascular invasion. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

 Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=13.517, df = 3, p = 0.004). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).

Multivariable analysis

Variables associated with LVI at p < 0.10, together with clinically relevant covariates, were entered into a multivariable model (SUVmax, pack-years, tumor size, sex, adenocarcinoma vs. other). Stage group and surgical approach, though significant on univariate analysis, were deliberately excluded: stage group partly overlaps with tumor size and represents a downstream measure of spread for which LVI is itself a contributing factor, and surgical approach was considered a surgical proxy rather than a biological determinant. SUVmax remained an independent predictor of LVI (adjusted OR = 1.083, 95% CI 1.048–1.119, p < 0.001), as did male sex (OR = 2.322, 95% CI 1.439–3.745, p < 0.001); pack-years, tumor size, and adenocarcinoma histology were not independently associated after adjustment, with tumor size attenuating from a significant crude effect (OR = 1.020, p < 0.001) to a non-significant adjusted effect (OR = 1.006, p = 0.321) (Fig. 3). The model was globally significant (omnibus p < 0.001) with modest explained variance (Nagelkerke R^2=0.166); Hosmer-Lemeshow indicated some lack of fit (p = 0.004). Crude and adjusted ORs are in Table 5.

Table 5
Univariate (Crude) and Multivariable (Adjusted) Logistic Regression Analysis for LVI (n = 478)

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
SUVmax	1.096 (1.065–1.127)	**< 0.001**	1.083 (1.048–1.119)	**< 0.001**
Pack-years	1.007 (1.000–1.013)	0.058	0.997 (0.990–1.005)	0.513
Tumor size (mm)	1.020 (1.010–1.030)	< 0.001	1.006 (0.994–1.017)	0.321
Sex (male vs female)	2.605 (1.698–3.996)	**< 0.001**	2.322 (1.439–3.745)	**< 0.001**
Adenocarcinoma (vs other)	0.593 (0.412–0.852)	0.005	0.966 (0.642–1.452)	0.867
Variables not included in the multivariable model				
Age	0.996 (0.978–1.015)	0.688	—	—
Comorbidity (yes vs no)	0.812 (0.497–1.328)	0.407	—	—
Neoadjuvant therapy (yes)	1.576 (0.782–3.179)	0.203	—	—
Surgical approach (ref: VATS)				
Thoracotomy vs VATS	1.757 (1.141–2.706)	0.011	—	—
Hybrid vs VATS	1.038 (0.644–1.674)	0.878	—	—
Stage group (ref: Stage I)				
Stage II vs I	3.277 (2.077–5.171)	< 0.001	—	—
Stage III vs I	2.489 (1.433–4.322)	0.001	—	—
Stage IV vs I	2.353 (1.051–5.270)	0.038	—	—

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
CI: confidence interval; OR: odds ratio; VATS: video-assisted thoracoscopic surgery; LVI: lymphovascular invasion. Crude OR was derived from univariate logistic regression models including each variable individually. Adjusted OR was derived from the multivariable model including SUVmax, pack-years, tumor size, sex, and histologic type (adenocarcinoma vs. other) simultaneously. —: variable not included in the multivariable model.				
Model fit: omnibus p < 0.001; Nagelkerke R²=0.166; Hosmer-Lemeshow p = 0.004.				
Surgical approach was not included in the multivariable model because it is considered a surgical proxy/confounder rather than a biological determinant of LVI (omnibus Wald p = 0.014).				
Stage group was not included in the multivariable model because it partly overlaps with tumor size (through the T component) and represents a downstream measure of anatomical tumor spread, for which LVI itself is a contributing factor; to avoid over-adjustment and collinearity, tumor size was retained as the more granular measure of local tumor burden (omnibus p < 0.001).				

Sensitivity and interaction analyses

As with STAS, excluding neoadjuvant-treated patients (n = 443) did not materially change the SUVmax–LVI association (adjusted OR = 1.082, 95% CI 1.046–1.120, p < 0.001), and the SUVmax × neoadjuvant interaction remained non-significant (Wald p = 0.604; LR χ^2=0.278, df = 1, p = 0.598).

Multicollinearity assessment

No problematic multicollinearity was observed among model covariates (all VIF < 1.4, tolerance > 0.70; highest condition index 7.67), consistent with the correlation pattern reported for STAS; the attenuation of tumor size after adjustment therefore reflects shared variance with SUVmax rather than statistical collinearity.

ROC analysis

ROC analysis demonstrated that SUVmax discriminated LVI-positive from LVI-negative cases with acceptable accuracy (AUC = 0.701, 95% CI 0.654–0.747, p < 0.001) (Fig. 4). The Youden-optimal cutoff was 4.85, corresponding to 85.7% sensitivity and 49.4% specificity. Together with the multivariable finding, this indicates that higher SUVmax is a clinically meaningful predictor of LVI, though the modest specificity suggests SUVmax is more useful for identifying low-risk than confirming LVI presence. As the cutoff was derived and evaluated within the same cohort, external validation is warranted.

Predictors of visceral pleural invasion (VPI)

Univariate analysis

Visceral pleural invasion was present in 202 of 478 patients (42.3%). Patients with VPI had higher SUVmax (11.24 ± 8.52 vs. 8.99 ± 7.50, p = 0.002) (Fig. 2) and larger tumor size (33.17 ± 19.55 vs. 27.99 ±

18.83 mm, p = 0.001) than those without. VPI was also associated with adenocarcinoma histology (47.9% vs. 35.6%, p = 0.007) and pathological stage (p < 0.001); neoadjuvant therapy showed a borderline association (57.1% vs. 41.1%, p = 0.064). Age, sex, comorbidity, pack-years, and surgical approach were not significantly associated with VPI (all p > 0.05). Detailed comparisons are in Table 6.

Table 6
Univariate Comparison of Categorical and Continuous Variables According to VPI Status (n = 478)

Variable / Category	VPI Negative (n = 276)	VPI Positive (n = 202)	p
Categorical variables, n (%)			
Sex			**0.637**
Female	75 (59.5)	51 (40.5)	
Male	201 (57.1)	151 (42.9)	
Comorbidity			**0.976**
No	44 (57.9)	32 (42.1)	
Yes	232 (57.7)	170 (42.3)	
Neoadjuvant therapy			**0.064**
No	261 (58.9)	182 (41.1)	
Yes	15 (42.9)	20 (57.1)	
Surgical approach			**0.454**
Thoracotomy	112 (54.9)	92 (45.1)	
Hybrid	81 (61.8)	50 (38.2)	
VATS	83 (58.0)	60 (42.0)	
Histologic type			**0.007**
Other	141 (64.4)	78 (35.6)	
Adenocarcinoma	135 (52.1)	124 (47.9)	
Stage group			**< 0.001**
I	179 (67.0)	88 (33.0)	
II	61 (51.7)	57 (48.3)	
III	27 (40.9)	39 (59.1)	

SD: standard deviation; SUVmax: maximum standardized uptake value; VATS: video-assisted thoracoscopic surgery; VPI: visceral pleural invasion. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

 Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=13.018, df = 3, p = 0.005). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).

Variable / Category	VPI Negative (n = 276)	VPI Positive (n = 202)	p
Categorical variables, n (%)			
Sex			**0.637**
IV	9 (33.3)	18 (66.7)	
Continuous variables, mean ± SD			
Age (years)	65.39 ± 10.12	65.74 ± 9.02	**0.538**
Pack-years	38.38 ± 25.97	41.28 ± 28.88	**0.560**
SUVmax	8.99 ± 7.50	11.24 ± 8.52	**0.002**
Tumor size (mm)	27.99 ± 18.83	33.17 ± 19.55	**0.001**

SD: standard deviation; SUVmax: maximum standardized uptake value; VATS: video-assisted thoracoscopic surgery; VPI: visceral pleural invasion. Categorical variables were compared using Pearson's chi-square test (Fisher's exact test where indicated); continuous variables were compared using the Mann-Whitney U test.

 Histologic type was categorized into four groups (adenocarcinoma / squamous cell carcinoma / neuroendocrine tumor / other) for descriptive purposes (χ^2=13.018, df = 3, p = 0.005). The p-value reported in the univariate table, and used for variable selection into the multivariable model, was derived from the binary recoding of histologic type (adenocarcinoma vs. other).

Multivariable analysis

Variables associated with VPI at p < 0.10, together with clinically relevant covariates, were entered into a multivariable model (SUVmax, tumor size, neoadjuvant therapy, adenocarcinoma vs. other); unlike the STAS and LVI models, pack-years was not entered as it did not meet the threshold for VPI (p = 0.560). Stage group, though strongly associated with VPI on univariate analysis (p < 0.001), was deliberately excluded because VPI is itself a component of the T-category (determining the T1→T2a threshold), and its inclusion would introduce circularity. SUVmax remained an independent predictor of VPI (adjusted OR = 1.044, 95% CI 1.015–1.073, p = 0.002), as did adenocarcinoma histology (OR = 2.478, 95% CI 1.629–3.771, p < 0.001) and tumor size (OR = 1.011, 95% CI 1.000–1.022, p = 0.042); neoadjuvant therapy was not independently associated after adjustment (OR = 1.815, 95% CI 0.882–3.738, p = 0.106) (Fig. 3). The model was globally significant (omnibus p < 0.001) with modest explained variance (Nagelkerke R^2=0.090); Hosmer-Lemeshow indicated good calibration (p = 0.398). Crude and adjusted ORs are in Table 7.

Table 7
Univariate (Crude) and Multivariable (Adjusted) Logistic Regression Analysis for VPI (n = 478)

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
SUVmax	1.036 (1.012–1.060)	**0.003**	1.044 (1.015–1.073)	**0.002**
Tumor size (mm)	1.014 (1.004–1.024)	**0.004**	1.011 (1.000–1.022)	**0.042**
Adenocarcinoma (vs other)	1.660 (1.148–2.401)	**0.007**	2.478 (1.629–3.771)	**< 0.001**
Neoadjuvant therapy (yes)	1.912 (0.954–3.834)	0.068	1.815 (0.882–3.738)	0.106
Variables not included in the multivariable model				
Age	1.004 (0.985–1.023)	0.697	—	—
Pack-years	1.004 (0.997–1.011)	0.250	—	—
Sex (male vs female)	1.105 (0.731–1.671)	0.637	—	—
Comorbidity (yes vs no)	1.008 (0.613–1.655)	0.976	—	—
Surgical approach (ref: VATS)				
Thoracotomy vs VATS	1.136 (0.738–1.750)	0.562	—	—
Hybrid vs VATS	0.854 (0.526–1.386)	0.523	—	—
Stage group (ref: Stage I)				
Stage II vs I	1.901 (1.222–2.958)	**0.004**	—	—
Stage III vs I	2.938 (1.690–5.108)	**< 0.001**	—	—
Stage IV vs I	4.068 (1.757–9.422)	**0.001**	—	—

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Variables included in the multivariable model				
CI: confidence interval; OR: odds ratio; VATS: video-assisted thoracoscopic surgery; VPI: visceral pleural invasion. Crude OR was derived from univariate logistic regression models including each variable individually. Adjusted OR was derived from the multivariable model including SUVmax, tumor size, adenocarcinoma (vs other), and neoadjuvant therapy simultaneously. —: variable not included in the multivariable model.				
Model fit: omnibus p < 0.001; Nagelkerke R^2=0.090; Hosmer-Lemeshow p = 0.398.				
Surgical approach was not included in the multivariable model because it is considered a surgical proxy/confounder rather than a biological determinant of VPI (omnibus Wald p = 0.455).				
Stage group was not included in the multivariable model because visceral pleural invasion is itself a component of the T-category in the AJCC staging system (determining the T1→T2a threshold); including stage group would therefore introduce circularity, with the outcome partly determining the predictor rather than the reverse (omnibus p < 0.001).				

Sensitivity and interaction analyses

As with STAS and LVI, excluding neoadjuvant-treated patients (n = 443) did not materially change the independent associations of SUVmax (adjusted OR = 1.034, 95% CI 1.005–1.064, p = 0.022), tumor size (OR = 1.015, 95% CI 1.003–1.027, p = 0.011), and adenocarcinoma histology (OR = 2.423, 95% CI 1.569–3.741, p < 0.001) with VPI (Hosmer-Lemeshow p = 0.476); the SUVmax × neoadjuvant interaction was again non-significant (Wald p = 0.184; LR χ^2=2.116, df = 1, p = 0.146).

Multicollinearity assessment

No problematic multicollinearity was observed among model covariates (all VIF < 1.4, tolerance > 0.70; highest condition index 5.57), the lowest collinearity profile among the three outcomes assessed, consistent with the correlation pattern reported for STAS.

ROC analysis

ROC analysis demonstrated that SUVmax discriminated VPI-positive from VPI-negative cases with weak accuracy (AUC = 0.584, 95% CI 0.532–0.635, p = 0.002), similar to STAS (Fig. 4). The Youden-optimal cutoff was 6.0, corresponding to 68.3% sensitivity and 45.3% specificity. Given this weak discrimination, SUVmax alone should not be used as a standalone classifier for VPI; as with STAS and LVI, the cutoff was derived within the same cohort, and external validation is warranted.

Discussion

In this retrospective cohort of 478 patients with surgically resected NSCLC, primary tumor SUVmax was independently associated with STAS, LVI, and VPI, even after adjustment for tumor size, histologic subtype, and other covariates. However, the strength of this association varied considerably: SUVmax showed acceptable discrimination for LVI (AUC = 0.701), but only weak discrimination for STAS (AUC =

0.578) and VPI (AUC = 0.584). SUVmax therefore appears to reflect, in part, the biological processes underlying these three invasion patterns, but captures this information most reliably for LVI, with limited standalone value for STAS and VPI.

The independent association we observed between SUVmax and STAS is consistent with previous reports [11, 12], which similarly identified SUVmax as a significant multivariable predictor of STAS. However, the AUC we observed (0.578) was substantially lower than the AUCs of up to 0.82 reported previously, likely because those studies combined SUVmax with additional CT-morphological or PET-derived features in a nomogram rather than evaluating it alone. This suggests SUVmax may be a useful component of a multivariable prediction model for STAS, but is unlikely to be sufficient as an isolated preoperative marker for this spatially defined phenomenon.

The association between SUVmax and LVI is consistent with prior work. Li et al. reported that SUVmax alone predicted LVI with an AUC of 0.675 in 161 surgically resected patients [14], comparable to our AUC of 0.701; notably, they found no significant difference between SUVmax and more complex volumetric parameters (MTV, TLG) requiring dedicated segmentation (all $p > 0.10$). This suggests SUVmax, a simpler metric already available in routine PET/CT interpretation, can match the discriminative performance of more resource-intensive volumetric measures. Male sex was also independently associated with LVI in our model; as its biological basis is unclear, this finding should be considered hypothesis-generating.

The independent association between SUVmax and VPI is consistent with prior reports. Tanaka et al. found SUVmax to be an independent predictor of VPI in 208 patients (adjusted OR = 1.09, 95% CI 1.02–1.16) [15], an effect size comparable to ours (adjusted OR = 1.044, $p = 0.002$). Adenocarcinoma histology was an even stronger predictor of VPI in our model (adjusted OR = 2.478, $p < 0.001$), suggesting histologic subtype captures part of the predisposition to pleural extension that SUVmax only partially reflects. Li et al. similarly reported that SUVmax was associated with a composite invasiveness measure (VPI, LVI, and lymph node metastasis) on univariate analysis, though it did not remain in their final multivariable model due to collinearity with a related metabolic ratio [13]. Together, these findings support SUVmax as a reproducible but modest correlate of VPI.

The biological basis for these associations likely relates to the link between tumor glucose metabolism and invasive phenotype. FDG accumulation in NSCLC correlates with overexpression of the glucose transporters GLUT-1 and GLUT-3 [16], and functional studies show that GLUT-3 is induced during epithelial-mesenchymal transition while GLUT-1 knockdown reduces migratory and invasive capacity in lung adenocarcinoma cells [17, 18]. This provides a plausible mechanistic chain linking SUVmax, as a surrogate for glucose transporter expression, to the invasion patterns examined here—although the modest and variable strength of these associations suggests SUVmax captures only part of a multifactorial process also involving histologic subtype, tumor size, and unmeasured molecular determinants.

These findings have several practical implications. Because SUVmax is already generated during routine preoperative PET/CT staging, it can contribute to risk stratification at no additional cost, though its weak-to-moderate discriminative performance (AUC 0.578–0.701) means it should not be used as a standalone classifier. Its value likely lies in a broader multivariable assessment alongside histologic subtype and tumor size, particularly for decisions on resection extent, since LVI independently predicts occult lymph node metastasis and influences the choice between sublobar resection and lobectomy with systematic dissection [19]. The high sensitivity of the LVI cutoff (85.7% at SUVmax ≥ 4.85) suggests SUVmax may be more useful for ruling out LVI than confirming it. VPI is a recognized high-risk feature that may prompt consideration of adjuvant chemotherapy [20], and a phase II trial has similarly suggested a potential benefit of adjuvant treatment in LVI-positive early-stage NSCLC [21]. A non-invasive, cost-free preoperative marker could help flag this possibility earlier in the diagnostic pathway, even without a highly specific threshold.

Limitations

This study has several limitations. It is a retrospective, single-center analysis, limiting generalizability; external validation of these findings, including the proposed SUVmax cutoffs, is needed before clinical application, ideally in a multi-institutional cohort. STAS, LVI, and VPI status were extracted from routinely issued pathology reports rather than a centralized, blinded re-review, and staining protocols (e.g., elastic stains for VPI) could not be standardized across cases. Because the cohort was accrued over five years, some variability in PET/CT scanner hardware or acquisition parameters cannot be excluded, and SUVmax in neoadjuvant-treated patients was measured on post-treatment restaging rather than pretreatment scans, although sensitivity analyses excluding these patients yielded consistent results. Finally, the discriminative performance of SUVmax was weak to modest for all three outcomes, and the relatively low Nagelkerke R^2 values indicate that unmeasured molecular, radiomic, or histological factors likely contribute additional predictive information beyond what was captured here.

Conclusions

In this large surgical cohort of NSCLC patients, primary tumor SUVmax was independently associated with STAS, LVI, and VPI, with the strongest discrimination observed for LVI. Because SUVmax is already available at diagnosis, it represents a cost-free component that could contribute to preoperative risk stratification alongside histologic subtype and tumor size. However, given its weak-to-moderate standalone performance, it should not replace multivariable assessment or postoperative pathological evaluation. Prospective, multi-institutional studies are needed to validate these findings and determine whether incorporating SUVmax into preoperative decision-making improves patient selection for resection extent, lymph node dissection, or adjuvant therapy discussions.

Declarations

Conflicting interests

The authors declare that there are no conflicts of interest related to the authorship or publication of this article.

Human ethics and consent to participate

All procedures performed in this research were in compliance with the ethical standards of the institutional and national research committees and with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal guardians. Ethical approval for this study was granted by the Ethics Committee for Medical Research at Ege University Faculty of Medicine. Ethical approval for this study was granted by the Ethics Committee for Medical Research at Ege University Faculty of Medicine (approval date: 01.10.2026; approval number: 26-10T/86).

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used generative AI and AI-assisted technologies to improve the language, readability, clarity, and organization of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Author Contribution

GKÖ; conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, AGE; conception and design, provision of study materials or patients, manuscript writing, final approval of manuscript, AKT; conception and design, provision of study materials or patients, manuscript writing, final approval of manuscript, HY; collection and assembly of data, manuscript writing, final approval of manuscript, TIA; provision of study materials or patients, manuscript writing, final approval of manuscript, KT; provision of study materials or patients, manuscript writing, final approval of manuscript, AC; provision of study materials or patients, manuscript writing, final approval of manuscript. UC; provision of study materials or patients, manuscript writing, final approval of manuscript.

Availability of data and materials

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

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Figures

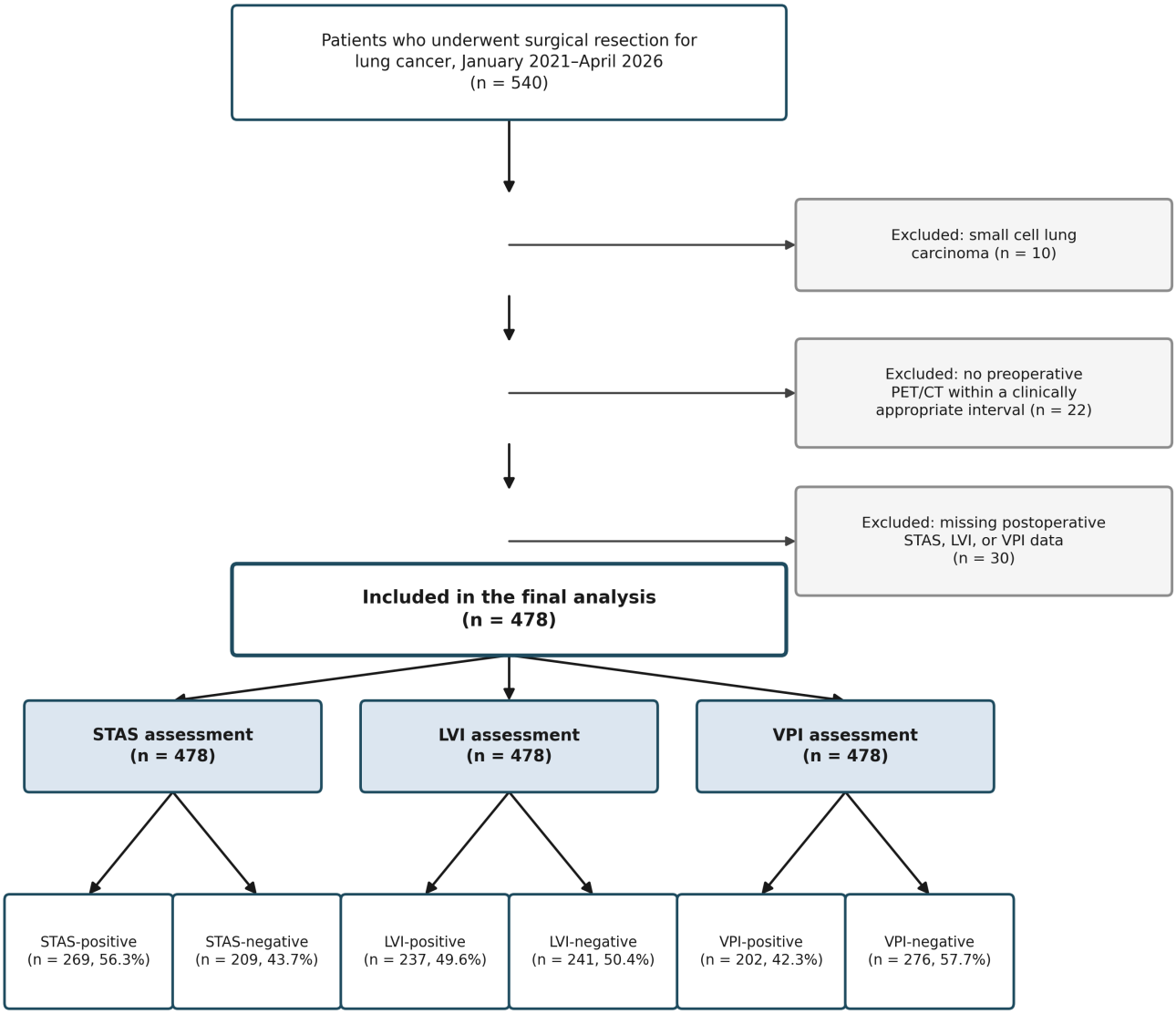


Figure 1

Flow diagram of patient selection

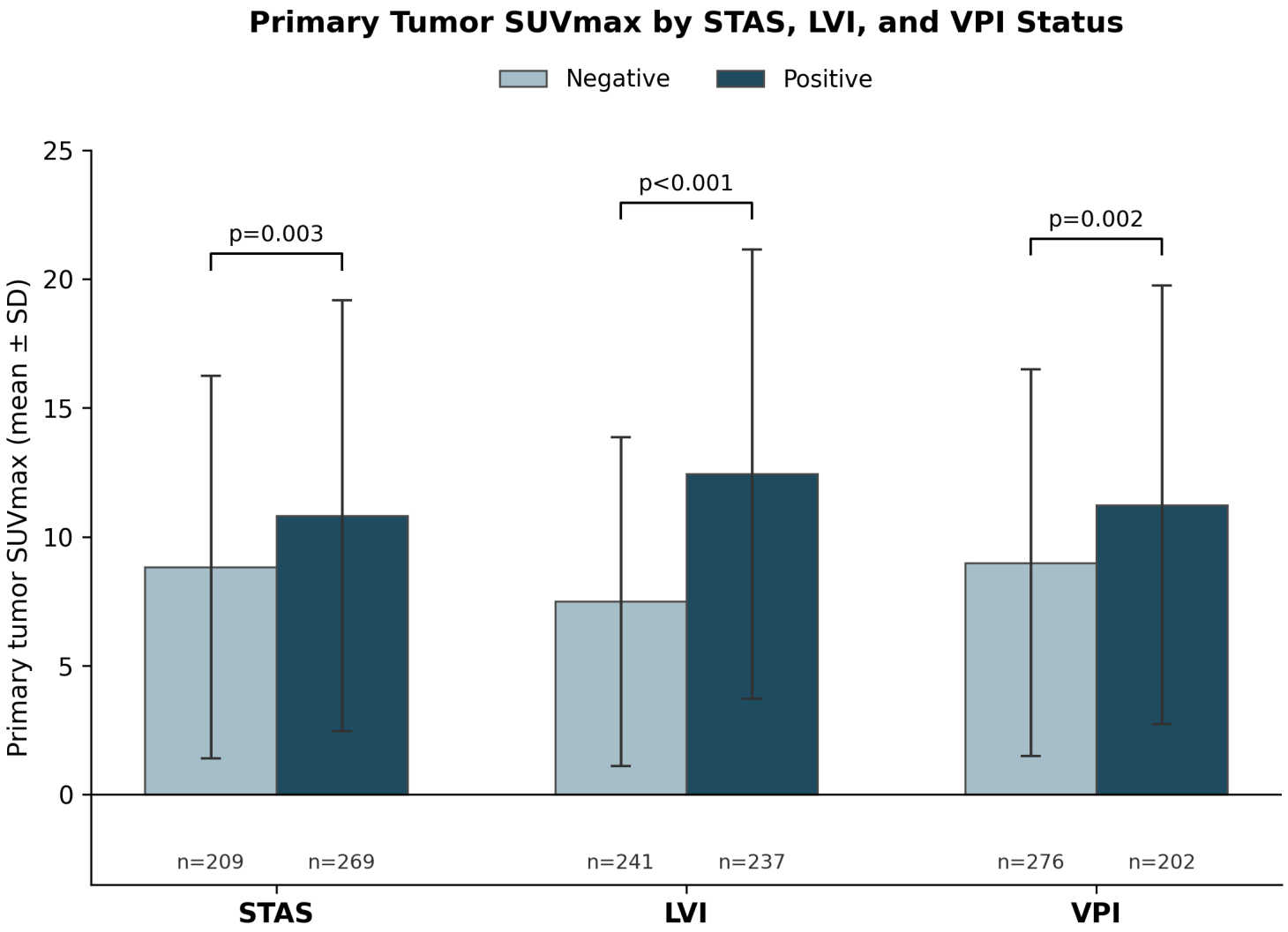


Figure 2

Primary tumor SUVmax according to STAS, LVI, and VPI status. Bars represent mean SUVmax; error bars represent ±1 standard deviation.

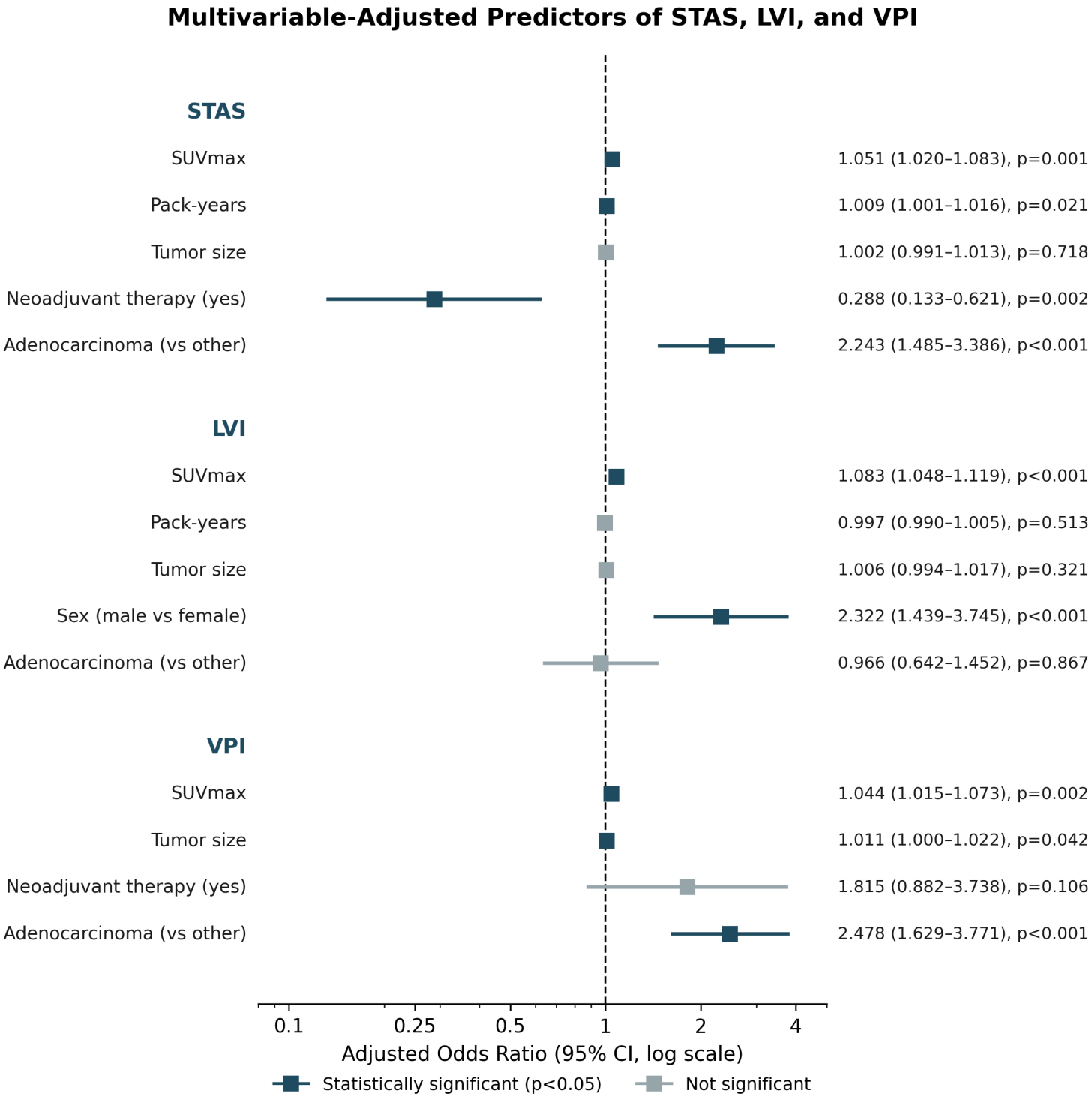


Figure 3

Forest plot of multivariable-adjusted odds ratios (ORs) for predictors of STAS, LVI, and VPI. Squares represent adjusted OR point estimates; horizontal lines represent 95% confidence intervals (CI). Teal markers indicate statistically significant associations (p<0.05); gray markers indicate non-significant associations. The dashed vertical line represents an OR of 1 (no association). The x-axis is displayed on a logarithmic scale.

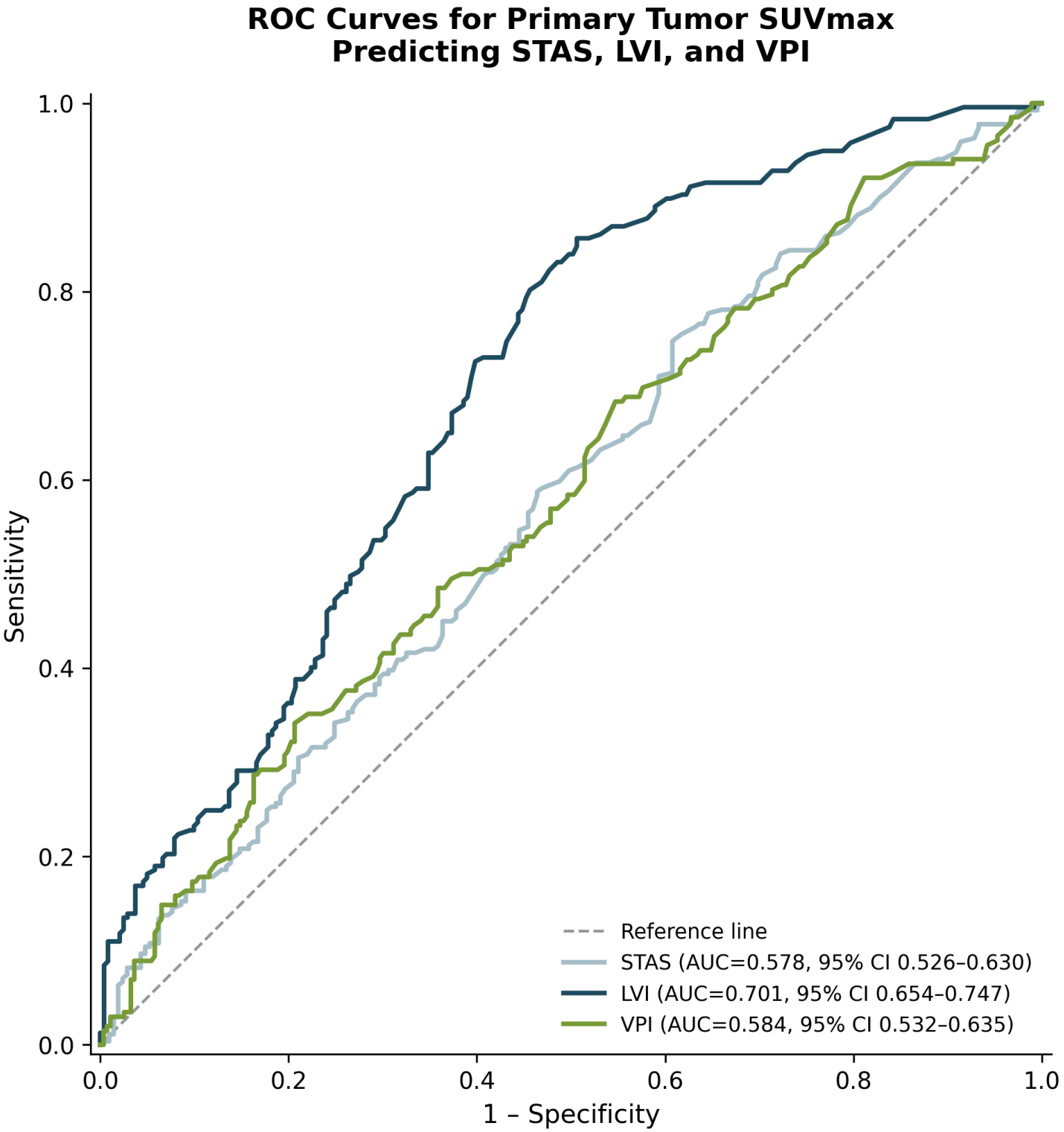


Figure 4

Receiver operating characteristic (ROC) curves for primary tumor SUVmax in predicting STAS, LVI, and VPI. The diagonal dashed line represents the line of no discrimination (AUC=0.5). AUC, area under the curve; CI, confidence interval.

Supplementary Files

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